Rejection under 35 U.S.C. §112, first paragraph

Applicants submit that the application is enabling for methods of transplanting retinal cells, as now claimed. The Examiner's rejection of the specification referred to unpredictability of the technique for implanting retinal cells and lack of guidance in the application. These points are discussed below with respect to the amended claims.

It should be noted that a preferred technique for transplanting retinal cells involves implanting cells directly in the eye, for example by injecting the isolated retinal stem cells or retinal cells differentiated from retinal stem cells into the vitreous of the eye. The cells for transplantation may be obtained from sphere colonies generated in culture that are dissociated and prepared as a cell suspension. These techniques are taught in the application and the knowledge in the art.

Alleged unpredictable nature of the invention

The Examiner provided four published papers describing alleged barriers for implementing retinal stem cell transplantation. The first barrier cited by the Examiner is immune rejection of transplanted tissue. In the first paper (Grisanti et al.), the Examiner cites work that provided evidence for rescue of degeneration-prone photoreceptor cells (in a RCS mutant rat model) by transplantation of normal retinal pigmented epithelial (RPE) cells. The article highlights the utility of this general transplantation approach. The Examiner focused on a statement made by the authors in their introduction that achieving long-term survival of RPE allografts remains elusive. The experiments in this paper demonstrated that transplantation in the subretinal space or the anterior chamber resulted in no acute immunological response of host tissue after 2 weeks and no delayed hypersensitivity. However, in the case of transplanted tissue to a site that is actively monitored by the immune system (subconjunctival space), there is a clear and significant immune reaction. The authors suggest that the body itself may

have a mechanism to prevent or at least substantially limit any potential immune reactions (ACAID) in specific regions of the eye that are "immune privileged." For Applicants' purposes, the region of the retina targeted with retinal stem cells and differentiated cells is protected and thus amenable to transplantation.

In the second paper cited by the Examiner (Enzmann et al.), the authors describe how human subretinal transplantation studies of embryonic or non-embryonic photoreceptor or RPE cells have been relatively unsuccessful compared to analogous studies in animal models, which have proven to be effective even after long periods of time. However, there have been comparatively few studies performed in humans and it is premature to suggest that this transplantation approach is not effective. In fact, on p.180 the authors describe experiments that have separated activated RPE cells (those expressing MHC II on their cell surface) from those that do not and demonstrate that selected transplanted RPE cells (non-activated) resulted in no significant immune response. It is also true that extensive immunosuppression can be detrimental for some patients, but short-term or long-term immunosuppression is a common intervention for all forms of organ transplantation (e.g. lung, liver, kidney) and in many cases without serious side effects. The extent of immunosuppression for patients with only tens of thousands of retinal stem cells and their progeny transplanted is likely to be minimal (at least compared to those patients whole receiving vital organs) and the concern for side effects may be negligible.

In the third paper cited (Crawford et al.), the Examiner states that the hurdle of immunological reactions must be overcome and that this paper corroborates the first two papers. The applicants respectfully disagree with the Examiner's position on this paper. The authors clearly state that graft failure is not due to immune infiltration, but rather on the action of macrophages and only in areas where the integrity of the transplanted tissue was compromised. The nervous system has a population of endogenous macrophages (microglia) that are involved in clearing cellular debris due to natural cellular attrition, in addition to being responsive in an

immune reaction with blood-borne immune cells. In this case, the death of photoreceptors may be due to the remodeling role of microglia to clear up cellular debris. Indeed, the lack of the major immune infiltrating cells in general and the lack of any evidence for an immune reaction where the tissue is intact suggests that rejection is not a significant barrier in this case. Modifying the parameters of the transplantation (e.g. number of cells transplanted) facilitates the integration of these cells in a more efficient monolayer with minimal or no damage due to loss of integrity and macrophage activity.

In the final paper cited (Valtink et al.), the Examiner again uses this paper as corroborating evidence for the conclusions drawn from the first two papers. This paper is about perfecting the culture conditions of RPE cells so that after they have been frozen and thawed they will demonstrate the same ability to be transplanted efficiently as freshly dissected tissue. This aids in the production and maintenance of a large supply of transplantable tissue. However, this paper does not appear to corroborate the Examiner's allegations with respect to the other papers discussed above.

In summary, the majority of transplant studies using animal models clearly demonstrate the feasibility and success of transplanting embryonic and non-embryonic RPE cells. Mitigating undesired immune reactions is not a significant barrier when dealing with transplanted RPE tissue in or near the retina (posterior compartment of the eye).

Alleged lack of guidance in the application

The specification and knowledge in the art provide guidance with respect to the procedures for transplanting the retinal stem cells and their progeny. As the Examiner mentioned on p.5, retinal stem cells are derived from RPE tissue. Further, the Examiner on page 3 acknowledges the ability to transplant RPE cells into mammalian eyes. Those skilled in the art are able to transplant retinal stem cells and their progeny just as efficiently as the more routine RPE transplants. As

discussed above, a preferred technique for transplanting retinal stem cells involves implanting stem cells directly in the eye.

Rejection under 35 U.S.C. §112, second paragraph

Claims 2-4 stand rejected under 35 U.S.C. §112, second paragraph, for indefiniteness; claims 2-4 have been cancelled. Accordingly, this rejection may be withdrawn.

Objection

Claim 1 was objected to due to informalities; claim 1 has been cancelled. Accordingly, this objection may be withdrawn.

CONCLUSION

Applicant submits that the grounds for rejection raised by the Examiner have been overcome, and that the claims, as amended, define an invention that is enabled and definite. Enclosed is a petition to extend the period for replying for three months, to and including January 17, 2001. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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